Lancashire and South Cumbria Haematology NSSG Guidelines for Diffuse Large B-cell Lymphoma (DLBCL)

1.0 Scope

This guideline does not apply to primary CNS or cutaneous, HIV-associated or post-transplant lymphoma, or transformed low grade lymphoma.

2.0 Pre-treatment and interim evaluation

2.1 The following tests should be performed:

- FBC, U&Es, creat, LFTs, calcium, LDH, urate
- Hepatitis B, C and HIV serology
- Chest X-ray
- PET-CT scan if feasible and where treatment is with curative intent. Otherwise contrast-enhanced CT scan neck, thorax and abdomen.
- MRI scan for assessment of disease in the oropharynx and Waldeyer's ring, sinuses and nasal cavity, and paraspinal areas where there is a suspicion of spinal cord compromise
- Consider bone marrow aspirate and trephine biopsy – although PET-CT has largely replaced routine marrow examination, it may miss low volume disease or low grade lymphoma hence biopsy may be indicated if this would influence management decisions regarding treatment decisions e.g change in prognostic score, staging of apparent early stage disease.
- CT +/- MRI scan brain and CSF exam where at high risk of CNS lymphoma
- Determination of Ann Arbor stage, presence of bulk disease >7.5cm, extranodal sites
- Determination of the R-IPI and NCCN-IPI or stage-modified IPI (smIPI) for limited stage disease (see appendices 1 and 2)
- Determination of the CNS-IPI (appendix 3)
- ECG and assessment of cardiac function in patients >60 years or with a history of or risk factors for cardiac disease or when mediastinal irradiation may be indicated

2.2 Interim and post-treatment evaluation

- There should be a formal assessment of response after four cycles of chemotherapy. If this cannot be done clinically e.g absence of palpable disease, a CT scan should be performed.
- On completion of treatment the patient must be reassessed clinically and, where treatment is given with curative intent, all abnormal tests at baseline repeated followed by MDT discussion with review of an end of treatment PET-CT scan performed at least 6 weeks after the last dose of chemotherapy, or three months after the last dose of radiotherapy.
- There should be rebiopsy or at least close follow up of residual FDG-avid lesions with repeat PET-CT scan before additional treatment.

3.0 Treatment

3.1 Stage I-II, no bulk (<7.5cm)

- R-CHOP x 3 cycles + 30Gy ISRT
- R-CHOP x 6 cycles +/- ISRT is an option where there is a concern regarding the potential toxicity of RT, if there are non-contiguous nodal areas, and according to prognostic factors such as presence of B symptoms, IPI score.
- A **PET-directed approach** is also appropriate: in patients who have a baseline PET-CT scan and smIPI 0-1. A PET-CT scan should be repeated in week 3 of cycle 4 R-CHOP. Metabolic CR is regarded as Deauville score <3:

  smIPI = 0 and in metabolic CR: no further treatment
  smIPI = 0 and in <metabolic CR: further RCHOP x 2 + 30Gy ISRT
  smIPI >0 and in metabolic CR: RCHOP x 2 then no further treatment
  smIPI >0 and in < metabolic CR: RCHOP x 2 + ISRT 30Gy
  if PD: treat as relapsed/refractory disease

3.2 Stage I-II, bulky (>7.5cm)

- RCHOP x 6 + 30Gy ISRT where feasible to sites of bulk or extranodal disease

3.3 Stage III-IV disease

- RCHOP x 6 + 30Gy ISRT where feasible to sites of bulk or extranodal disease
- For patients with a high risk IPI and where the risk of CNS relapse is high the option of R-CODOX-M/R-IVAC should also be considered.

3.4 Primary mediastinal B-cell lymphoma

- **O**ptions are RCHOP 14 x 6 cycles +/- ISRT
- or dose-adjusted R-EPOCH x 6 cycles if the toxicity of consolidation RT is a concern.
- Note that consolidation RT does improve outcomes in patients treated historically with CHOP alone. However, it remains unclear whether RT can be safely omitted in patients who are in metabolic CR after R-CHOP or R-EPOCH. The role of RT must be discussed at the MDT with the radiation oncologist after consideration of metabolic response, role of re-biopsy of residual lesions, risk of RT toxicity and patient choice.
- Relapse should be treated as for relapse of DLBCL

3.5 DLBCL at special sites

- DLBCL of testis stage I-IV: orchidectomy followed by RCHOP x 6 + CNS prophylaxis (see 3.9) + prophylactic RT to contralateral testis (and to sites of pelvic disease for stage II).
- Extranodal sites: RCHOP x 6 + 30Gy ISRT to extranodal disease where feasible e.g bone, gastric

3.6 'Double hit' lymphomas

- The finding of 'double' or 'triple hit' DLBCL must be interpreted in the context of the IPI score - R-CHOP remains appropriate for low and low-intermediate score patients
- The prognosis for 'double hit' treated with R-CHOP has been associated with poor outcomes but it remains unclear whether this is improved with more intensive chemotherapy.
- If feasible the option alternatives to RCHOP should be discussed with the patient e.g R-EPOCH x 6 cycles or, in the presence of CNS disease, R-CODOXM/R-IVAC x 2 cycles.
- Note there is a higher risk of CNS relapse therefore CNS prophylaxis should be offered
- Consolidation RT should be considered as for other DLBCLs.

3.7 Patients not fit for full-dose RCHOP

- Note that it is possible to give full-dose R-CHOP21 to many elderly patients with good performance status and adequate cardiac function, especially when given with primary GCSF prophylaxis, and full-dose therapy is associated with improved outcomes.
- Options are:
  - 50% R-CHOP21 x 3-6 cycles (mini-RCHOP) according to stage
  - Where cardiotoxicity is a concern consider a modified RCHOP21 with etoposide in place of doxorubicin (R-CEOP)
  - Consider RT to sites of bulk, extranodal or residual disease depending on age, performance status and sites of disease
  - For frail patients consider CVP, low dose oral etoposide +/- steroids or oral DECC, palliative RT, palliation alone.

3.8 Radiotherapy consolidation

- The use of consolidation RT should be decided at the MDT on a case by case basis in conjunction with a radiation oncologist.
- Selected stage I-II, non-bulky patients may be spared additional treatment with RT if in metabolic CR after RCHOP x 4 cycles (see 3.1 PET-directed therapy).
- The role of PET-directed consolidation RT to residual metabolic abnormalities or to guide the use of RT to sites of initial bulk or extranodal disease remains unclear. Decisions must be made at the MDT in conjunction with a radiation oncologist on a case by cases basis.

3.9 The role of CNS prophylaxis

- Indications for CNS prophylaxis will be reviewed and a decision made at the MDT on a case by case basis after consideration of stage, IPI, sites of disease, IPI and CNS-IPI score.
- A CSF cytospin will be examined in patients considered high risk.
- CNS prophylaxis should be offered to patients with:
  - a high-risk CNS-IPI score (4-6)
  - involvement of ≥ 3 extranodal sites irrespective of the CNS-IPI score
  - certain anatomical sites: testicular, renal/adrenal, breast

- CNS prophylaxis should also be considered for patients with disease involving the breast or uterus.
- The preferred mode of prophylaxis is IV high dose methotrexate at least 3g/m^2 over 4 hours for 2-3 cycles but the patients performance status and fitness, renal and cardiac function must be considered.
- Since the majority of CNS relapse occur early in the disease course, prophylaxis should be given early during initial chemotherapy. It is possible to intercalate high dose methotrexate with R-CHOP i.e given on day 8-12, and this is the preferred approach. Where this is not possible high dose methotrexate should be given after completion of the R-CHOP course and in the interim the use of intrathecal methotrexate with cycles 1-4 R-CHOP must be considered in high risk cases e.g testicular.
- If it is not possible to give high dose methotrexate, intrathecal chemotherapy with methotrexate should be offered.

4.0 Management of relapse and refractory disease

4.1 Pre-treatment assessment

- For patients relapsing from CR repeat biopsy should be considered, especially for late relapsed and where high dose therapy is an option
- Patients should be restaged with a PET scan or if this is not possible with a CT scan and bone marrow examination if considered fit enough for high dose therapy.
- The second-line age-adjusted IPI (appendix 4) and time to relapse from CR must be calculated for patients considered fit for transplant.

4.2 Treatment if a candidate for high dose therapy

- Initial treatment should be 2 cycles of salvage chemotherapy
- Salvage regimen will generally be R-ICE, R-DHAP or R-GEM-P according to patient factors/comorbidities and feasibility of local treatment
- After cycle 2 the patient must be reassessed clinically and with a CT scan, and if in PR/CR a third cycle can be given with a view to PBSC mobilisation
- In week 3 of cycle 3 a PET-CT scan will be repeated.
- If in a metabolic CR and with adequate performance and organ function offer consolidation with LEAM and autologous stem cell transplant.
- If a metabolic CR has not been achieved the significant negative impact on prognosis must be discussed with the patient. Autologous transplant remains an appropriate option however, the patient should be appraised of alternatives e.g CAR-T cell therapy, referral for consideration of experimental treatments or allogeneic transplantation.
- In patients who fail to respond to initial salvage chemotherapy an alternative salvage chemotherapy should be considered but it must be recognised that very few such patients respond sufficiently to allow consolidation with autologous transplant. CAR-T cell therapy if eligible or referral for experimental and novel therapies may be more appropriate.

4.3 Treatment if not a candidate for autologous stem cell transplant including relapse following transplant

- Treatment choice will depend on age, performance status, comorbidity, previous treatments, access to clinical trials and compassionate use programmes, eligibility for CAR-T cell therapy.
- Note that CAR-T cell therapy may be appropriate for older patients e.g >70 years, or those with significant comorbidities for whom from autologous transplant would not usually be considered.
- Chemotherapy treatment options are single agent gemcitabine, or gemcitabine combinations e.g R-Gem-Ox, pixantrone, low dose oral etoposide +/- steroids, DECC, lenalidomide, palliative RT.

Appendices

Appendix 1: IPI, age-adjusted IPI, R-IPI and NCCN-IPI for diffuse large B-cell lymphoma

IPI (pre-rituximab era) and R-IPI (rituximab era) risk factors:

- age > 60yrs
- stage III/IV
- raised LDH
- ECOG >=2
- 1 site of extranodal disease.

For age-adjusted IPI (more predictive in patients <60ys):

- stage III/IV
- raised LDH
- ECOG>=2

IPI and age-adjusted IPI

	all ages	age <60yrs
low risk	0-1	0
low-intermediate risk	2	1
high-intermediate risk	3	2
high risk	4-5	3

Overall survival at 5 years according to IPI

low	73%	83%
low-int	51%	69%
high	43%	46%
high-int	26%	32%

Overall and PFS at 4 years according to R- IPI

	PFS	OS
Very good	94%	94%
Good	80%	79%
Poor	53%	55%

Overall and PFS at 4 years according to R- IPI

	PFS	OS
Very good	94%	94%
Good	80%	79%
Poor	53%	55%

NCCN-IPI

		Score
Age	>40 <60y	1
	>60 ≤ 75y	2
	>75y	3
LDH	>1 ≤ 3 x ULN	1
	>3 x ULN	2
Stage III-IV		1
ECOG ≥2		1
Extranodal site*		1

*lung, liver, GIT, CNS, marrow

Risk groups

Score	Risk	5y OS
0-1	Low	96%
2-3	Low-intermediate	82%
4-5	High-intermediate	64%
≥6	High	33%

Appendix 2: Stage-modified IPI for limited stage DLBCL

Risk factors are:
Age >60yr, high LDH, ECOG score >0, stage II

Appendix 3: CNS IPI risk score (Schmitz et al 2016)

Risk factors: age >60yr
high LDH
stage III/IV
ECOG score >1
1 site of extranodal disease
Presence of renal/adrenal disease

Risk of CNS relapse		
Low	0-1	<1 % risk
Intermediate	2-3	3-4%
High	4-6	10-12%

Appendix 4: Second line age adjusted IPI in relapsed diffuse large B-cell lymphoma in the prediction of outcome for autologous stem cell transplantation for relapsed and refractory diffuse large B-cell lymphoma (Hamlin et al, Blood 2003)

Relapsed DLBCL, all treated with ICE. Age adjusted IPI calculated at initiation of second line therapy

Risk factors: LDH, stage III/IV, performance status (ECOG≥ 2)

Factors		**PFS**	**OS**
0	Low	70%	74%
1	Intermediate	39%	49%
2-3	High	16%	18%

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